

REMARKS**35 U.S.C. § 103(a) (Obviousness)**

Claims 1, 4, 5, 7-11, 13-15, 17, 18, 20-21, 24-26, 28-31, 34-35, 38-40, 42, 43, and 46-50 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 6,403,091 to Lederman et al. ("Lederman") in view of U.S. Patent No. 5,597,563 to Beschorner et al. ("Beschorner") and U.S. Patent No. 6,056,956 to Cobbold et al. ("Cobbold") and in further view of U.S. Patent No. 4,959,302 to Cornaby et al. ("Cornaby"), for the reasons stated in the Office Action.

Applicants respectfully traverse this rejection, for the reason that no combination of the cited references would have given the skilled artisan guidance to induce T cell non-responsiveness to an allogeneic or xenogeneic donor tissue or organ in a human recipient comprising administering (a) a donor cell and (b) an anti-human gp39 antibody, or human soluble CD40 molecule in a five to eight day period prior to transplantation. Administration of anti-CD40 tolerizing agents within a five to eight day period prior to graft transplantation is not taught or suggested by any combination of the above-cited references.

Lederman describes antibodies to a T-cell antigen (5c8) which inhibit T-cell activation of B-cells. Lederman does not teach or suggest any method or time frame for administration of tolerizing agents prior to transplantation; therefore, Lederman does not make obvious the treatment or time frames of the methods of the claims.

Beschorner teaches induction of antigen-specific tolerance by administration of Antigen Presenting Cells (APCs). The Examiner cites Beschorner as teaching a 7 to 28 day administration of an immunosuppressive agent prior to administration of APCs. Office Action at 2. Applicants respectfully fail to see how administration of an *immunosuppressive agent* (in Beschorner, cyclosporine) relative to administration of a *tolerizing agent* (tolerogenic APCs) guides the skilled artisan in administration of a *tolerizing agent* (in the instant application, donor cells plus a CD40-L inhibitor, which are roughly equivalent to the immunosuppressive agent *and* the tolerizing agent of Beschorner) relative to administration of a *tissue graft*. Beschorner does not teach administration of tolerizing agents in any time frame relative to when the actual donor organ or tissue is transplanted. Therefore, Beschorner cannot make obvious the five to eight day treatment period of

The Examiner contends that the five to eight day administration of tolerizing agents “appears well within the variable of an immunosuppressive regimen that achieved a recognized result of inhibiting or preventing graft rejection[.]” Office Action at 3. However, the Examiner does not provide a single immunosuppressive regimen for administration of tolerizing antibodies and antigen relative to transplant of donor tissues, let alone a treatment regimen that results in inhibiting or preventing transplant rejection. The Examiner further states that “The ordinary artisan provided immunosuppression prior, during, and after transplanting grafts of interest, including encompassing the newly amended regimen.” Office Action at 3. Applicants respectfully submit that the Examiner has not provided evidence in support of this statement. In particular, no evidence has been provided that encompasses the regimen as set forth in the claims. Nor does “monitoring impending rejection” have any relation to the administration of the tolerizing regimen of the claims prior to transplant of donor tissue. Monitoring impending rejection takes place following transplantation, not before. Therefore no suggestion for administration prior to transplantation can be afforded by indications of treatment that rely on measurements taken after transplantation. Office Action at 3.

The time frame for administration of the tolerizing agents of the claims represents a significant difference in the method of tolerizing transplant recipients, a time frame which is in no way provided in the cited references. Prior to the disclosure of the instant invention, one of skill in the art attempting to tolerize an individual using an immunosuppressive agent would lack guidance as to the critical time frame and sequence for applying donor cells and gp39 antibodies as an immunosuppressive agent, relative to transplantation of the donor tissue, in order to achieve success. Using the methods of the invention as claimed, such a skilled artisan now has the tools in hand to properly tolerize a patient in need of an organ transplant using the gp39 antibodies of the invention.


In contrast to the Examiner’s assertions, neither Beschorner nor Cobbold teach administration of antigen and/or antigen-expressing APCs in a five to eight day period prior to transplantation. Office Action at 3. Therefore, no combination of the above-cited references teaches or suggests the claimed methods. The cited references do not teach or suggest each and every element of the claimed invention; therefore, a *prima facie* case of obviousness has not been made.

CONCLUSION

Applicants respectfully request entry of the foregoing remarks. If any points remain in issue, Applicants hereby request an interview with the Examiner to further prosecution of this application.

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Respectfully submitted,

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